REMARKS

Applicants thank the Examiner for withdrawal of rejections under 35 U.S.C. § 112 ¶2 in view of Applicants' responsive Amendment, filed 05 September 2002.

Claims 1-4, and 7-12 are pending (previously restricted to SEQ ID NOS:34-38), claims 5 and 6 having been cancelled without prejudice, the limitations thereof having been recited in *independent* claim 1 (Previously amended).

Applicants acknowledge the Examiner's maintained rejections under 35 U.S.C. § 112 *first* and *second* paragraphs, and under 35 U.S.C. § 102. Applicants acknowledge the Examiner's new grounds of rejection, based on alleged new matter.

Applicants have responsively amended the pending claims to remove the alleged new matter and bring the scope of the claims into conformity with the specification in view of the Examiner's comments.

Applicants have attached hereto the Affidavit of Dr. Cathy Lofton-Day in support of the inventive diagnostic utility.

Applicants respectfully request reconsideration of the above-identified patent application in view of the current amendments and following remarks. Applicants respectfully request entry of the present responsive Amendment , and allowance of all pending claims 1 (Currently amended), 2 (Currently amended), 4 (Previously amended), 7 (Currently amended), 8 (Previously amended), 9 (Currently amended), 10 (Currently amended), 11 (Original) and 12 (Original).

No new matter has been added.

New Matter Rejection

The Examiner rejected claims 1-4 and 7-12 under 35 U.S.C. § 112, ¶1, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention" (Office action of 25 November 2002, at page 2, para 4).

Specifically, the Examiner asserts that the specification does not provide a basis for a claim limitation of 'at least 98% identical to SEQ ID NOS:34-38,' that goes beyond the scope of the multiple sequences already encompassed by each of the SEQ ID NOS:34-38 by virtue of the variable "n" positions therein.

Applicants have further amended independent claims 1, 2, 7, 9 and 10 to delete the phrase

"least 98% identical to SEQ ID NOS:34-38," and independent claim 1 now recites a "DNA sequence selected from the group consisting of SEQ ID NOS:34-38...."

Applicants have cancelled claim 3, in view of the above amendments, and in view of further amendments described herein below.

Applicants, therefore, respectfully request withdrawal of the Examiner's new matter rejection with respect to pending claims 1, 2, 4, and 7-12.

Claim Objection

The Examiner objected to claim 9, under 37 C.F.R. § 1.75(c), "as being of improper dependent form for failing to further limit the subject matter of a previous claim" (Office action of 25 November 2002, at page 3, para 5).

Applicants respectfully traverse this claim objection, based on the fact that claim 9 recites "probe or primer comprises at least 12 contiguous nucleotides *of* a sequence...." (emphasis added), whereas independent claim 7 recites "probe of primer which *hybridizes to* any region of at least 12 contiguous nucleotides of a sequence..." (emphasis added). Thus, independent claim 7 encompasses probes or primers that hybridize, despite having, *e.g.*, a single nucleotide mismatch with the target, and thus is broader in scope that dependent claim 9 that recites primers and probes having identical sequence to at least 12 nucleotides of the target.

Applicants, therefore, respectfully request withdrawal of this claim objection.

Rejections under 35 U.S.C. § 112, ¶1

Written Description:

The Examiner rejected claims 1-4 and 7-12 under 35 U.S.C. § 112, ¶1, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention" (Office action of 25 November 2002, at page 3, para 6).

First, the Examiner, citing *The Regents of the University of California v. Eli Lilly* 43 USPQ2d 1398-1412 (Fed Cir. 1997), alleg es that while the claims recite a genus of "DNA sequences having at least 90% identity with SEQ ID NO:34-38, CpG island sequences associated with SEQ ID NO:34-38, CpG island sequences associated with sequences having a nucleotide sequence at least 90% identical to SEQ ID NO:34-38, and combinations thereof," "applicants have

not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus" (*Id*, at page 4).

Second, the Examiner asserts that "the specification does not appear to define what 'associated' means in a clear and definite way" (*Id*, at page 5).

Applicants, as described above in response to the Examiner's new matter rejection, have further amended independent claims 1, 2, 7, 9 and 10 to delete that phrase "least 98% identical to SEQ ID NOS:34-38," and independent claim 1 now recites a "DNA sequence selected from the group consisting of SEQ ID NOS:34-38...."

Applicants reiterate that the relevant identifying characteristics of applicants' "associated" CpG-island sequences are clearly defined in the specification (*see* Specification; definition of CpG island at page 4, line 36 to page 5, line 5). Moreover, inclusion of such associated CpG island sequences within the claim scope is entirely supported by the specification, which states the art-recognized principal that "the methylation state of a portion of a given CpG island is generally representative of the island as a whole...." (*see* Specification at page 8, lines 22) (*see also* Liang et al., *Cancer Research* 60:4907-4912 (01 September 2000), at the first column of page 4911; already of record).

Nonetheless, in response to the Examiner's concerns, applicants have further clarified the claimed subject matter by further amending independent claim 1 and dependent claim 2 by deleting the word "associated," and by reciting "CpG island sequences contiguous with, or encompassing at least one nucleotide of SEQ ID NOS:35-38, wherein a CpG island sequence is a contiguous sequence of about 0.2 to about 1 kb in length that satisfies the criteria of having both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6, and a GC Content >0.5.

Support for this amendment is described above, and is also found under the definition of CpG island in the specification at page 4, line 36 through page 5, line5. These limitations provide adequate structure, in view of the above-described art-recognized principle, to the subject CpG islands, because said islands, as would be obvious to one skilled in the art, either encompass all or a portion of SEQ ID NOS:34-38, or are immediately adjacent to SEQ ID NOS:34-38 on the respective chromosomes. That is, the subject CpG islands are those genomic CpG islands that comprise, to some extent, at least one of SEQ ID NOS:34-38 and thus would be reasonably expected to reflect the methylation status thereof.

Applicants, in view of the above-described amendments, respectfully request withdrawal of the Examiner's 35 U.S.C. § 112, ¶1 (written description) rejection with respect to claims 1, 2, 4, and 7-12.

Enablement:

The Examiner rejected claims 1-4 and 7-12 under 35 U.S.C. § 112, ¶1, "as containing subject matter which was not described in the specification in such a way as to *enable* one skilled in the relevant art to make or use the invention (Office action of 25 November 2002, at page 8, para 7).

Specifically, and *first*, the Examiner maintained the allegation that applicants' own statements in the specification undermine and contradict the claimed utility (*Id*, citing, *inter alia*, the instant specification at page 2 lines 31-35).

Specifically and *second*, the Examiner maintained the assertion that the specification teaches that SEQ ID NOS:34-38 are hypermethylated as opposed to hypomethylated, whereas the claims recite broader language that includes hypomethylation (*Id*, at page 10).

Specifically, and *third*, the Examiner maintained the assertion that the disclosed methylation analyses relating to SEQ ID NOS:34-38 were performed *only* in the context of prostate and bladder cancer tissue, and therefore do not enable diagnosis of any and all cancers, based on the same methylation differences (*Id*, at page 11).

Specifically, and *fourth*, the Examiner maintained the allegation that the specification has not taught a predictable correlation between nucleic acids which are *associated* with SEQ ID NOS:34-38' (*Id*).

Applicants reiterate their previous responses to these assertions, and respectfully traverse the Examiner's above-described rejections with respect to the ***first*** and ***fourth*** assertions, based on the teachings of applicants' originally filed specification, and the knowledge and skill in the relevant art at the time of filing.

First, with respect to the Examiner's *first* assertion, applicants firmly maintain the contention that the Examiner has inappropriately misconstrued applicant's quoted statements. In fact, applicant's statement at issue on page 2 of the specification says that the mere knowledge that any (any unidentified sequence or gene) altered methylation states exist, or that methylation can affect particular gene expression, in the abstract sense, does not enable detection, and that this

altered methylation state (or altered expression) must be correlated to ***specific*** sequences or genes, and in turn correlated with cancer. This is in fact what applicants have accomplished in the instant invention. This statement was part of applicants' "Background" section, and the intended meaning is clearly to indicate that methylation analyses and correlations need to be made with ***specific*** sequences or genes. Applicants respectfully contend that the Examiner's position is inappropriate in view of the clear and reasonable context of the phrases at issue.

Applicants reiterate that in fulfillment of this need, applicants' specification teaches and discloses altered methylation states of *particular* sequences and correlates these *particular* markers with cancer, and in particular with bladder and prostate cancer. Applicants are not required to show that such altered methylation is *causative* of cancer, but rather show, as has in fact been determined, that a distinguishing (with respect to normal tissue) association or correlation exists between the methylation state of particular CpG dinucleotide sequences and cancer.

Second, with respect to the Examiner's *second* assertion, applicants have previously amended (see applicants responsive amendment of 05 September 2002) step (c) of *independent* claim 1 to recite "determining a diagnosis or prognosis based, at least in part, upon the methylation state of the CpG dinucleotide within the DNA sequence, wherein the determined methylation state is either hypermethylation or normal methylation." The Examiner failed to consider this amendment in the present Office Action, and applicants respectfully contend that this issue has been adequately addressed.

Third, with respect to the Examiner's *third* assertion, applicants have cancelled *dependent* claim 6, and further amended step (c) of *independent* claim 1 to delete "bladder."

Fourth, with respect to the Examiner's *fourth* assertion, applicants have, as described in detail above in response to the Examiner's Written Description based rejection, clarified the nature of applicant's recited "associated" CpG island sequences, and has cited support in the specification and prior art (including applicants' own literature publication that is of record).

AFFIDAVIT of Dr. Cathy Lofton-Day:

Finally, in confirmation of the general diagnostic utility taught and enabled by the instant invention, applicants attach hereto the Affidavit of Dr. Cathy Lofton-Day (of Epigenomics, Inc., Seattle, WA.) who is an internationally recognized expert in the field of diagnostic assays based

on differentially methylated CpG dinucleotide sequences. The *curriculum vitae* of Dr. Lofton-Day is attached to the Affidavit as APPENDIX A.

Significantly, Dr. Lofton-Day has overseen experiments using the MS-APPCR assay (the same assay described in the present specification) and the present marker sequences, and that involve multiple experiments and multiple tissue samples, and which confirm the inventive general diagnostic utility as originally taught and enabled by the present specification.

Independent claim 1 has been appropriately amended by deleting "bladder" (as described above), and reciting "breast" and "colon," in addition to prostate cancer.

Applicants, therefore, respectfully request withdrawal of the Examiner's 35 U.S.C. § 112, ¶1 (enablement) rejection with respect to claims 1, 2, 4, and 7-12.

Rejections under 35 U.S.C. § 102

The Examiner's rejection of claims 7-9 under 35 U.S.C. § 102 as being anticipated by Herman et al. (US Pat. 5,786,146, July 28, 1998) was maintained (*see* Office Action of 25 November 2002, at page 14).

Specifically, the Examiner maintains that the primer corresponding to SEQ ID NO:46 of Herman et al. would hybridize to nucleotides 212-219 (8 nucleotides) of applicant's SEQ ID NO:34 sequence, and thus comprise at least about 12 nucleotides which are at least about 90% identical to applicant's SEQ ID NO:34. Alternatively, the Examiner asserts that the Herman et al. primer comprises 10 nucleotides which are 90% identical to SEQ ID NO:34 (*Id*).

Applicants have, in response to the Examiner's maintained comments, amended independent claim 7 to recite "probe or primer which hybridizes to any region of at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOS:34-37, and 38"

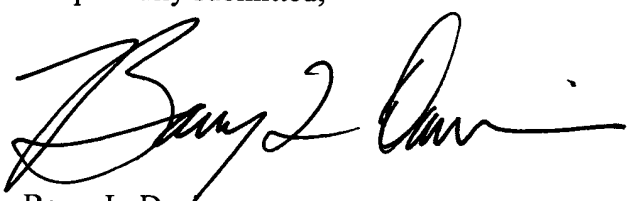
These amendments distinguish the present invention from that of Herman et al. by requiring hybridization to at least a 12 nucleotide *contiguous* region. The amendments are supported, *inter alia*, by the originally filed claims, and in particular claim 9. No new matter has been added.

Applicants, therefore, respectfully request withdrawal of the Examiner's 35 U.S.C. § 102 anticipation rejection under Herman et al. with respect to claims 7, 8, and 9.

Conclusion

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration of the claimed invention, entry of the present responsive Amendment and allowance of all pending claims 1 (Currently amended), 2 (Currently amended), 4 (Previously amended), 7 (Currently amended), 8 (Previously amended), 9 (Currently amended), 10 (Currently amended), 11 (Original) and 12 (Original).

Respectfully submitted,



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